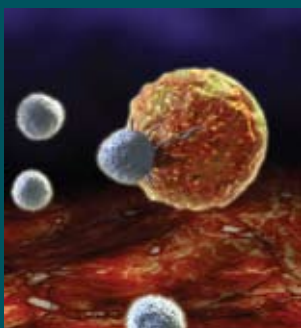


Breast Cancer Research Program



U.S. Army Medical Research and Materiel Command



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Congressionally Directed Medical Research Programs



VISION

Find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public.

MISSION

We provide hope by promoting innovative research, recognizing untapped opportunities, creating partnerships, and guarding the public trust.

HISTORY

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was born in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public,

Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received \$6B in appropriations from its inception through fiscal year 2010 (FY10). Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs, such as the Breast Cancer Research Program (BCRP) is allocated via specific guidance from Congress.

PROPOSAL REVIEW PROCESS

The CDMRP uses a two-tier review process for proposal evaluation, with both tiers involving dynamic interaction among scientists and disease survivors. The first tier of evaluation is a scientific peer review of proposals measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Integration Panel (IP), which is composed of leading scientists, clinicians, and consumer advocates. The IP compares proposals to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to program goals.



The BCRP fills important gaps not addressed by other funding agencies in support of breast cancer research. The BCRP funds groundbreaking, high-risk, high-gain research and encourages out-of-the-box thinking.

Breast Cancer Research Program

VISION

To eradicate breast cancer by funding innovative, high-impact research through a partnership of scientists and consumers.

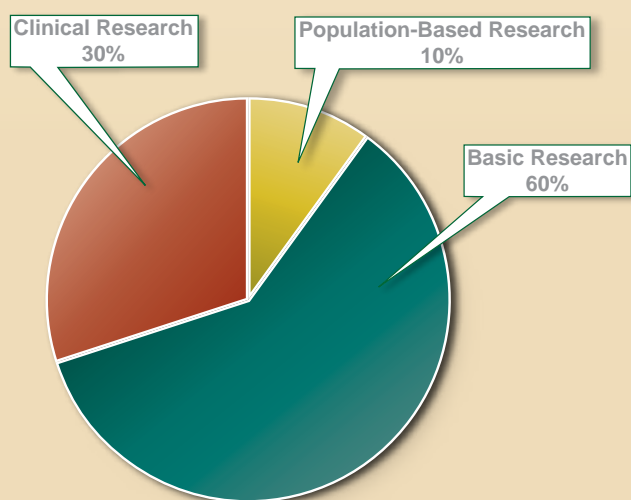
ABOUT THE PROGRAM

Since the BCRP was established in 1992, the dedicated efforts of breast cancer advocates have resulted in more than \$2.5 billion in appropriations to the program, including \$150 million in fiscal year 2010 (FY10). The BCRP vision is adapted yearly to facilitate rapid change and to ensure that the program remains responsive to what is currently happening in the research community. The BCRP has created and introduced unique mechanisms to support a broad portfolio of research and training awards that have transformed the breast cancer field. The BCRP challenges scientists to pursue high-risk research that has the potential to make major leaps forward in breast cancer. The program is committed to supporting new, innovative ideas that reflect the most recent discoveries in the field and could lead to breakthroughs. The BCRP training and early-career awards have provided the foundation for many of today's leading breast cancer researchers, and the program continues to invest in the future generation of breast cancer experts. Recognizing the need to promote team science, the BCRP also created unique award mechanisms that foster synergistic partnerships among scientists from different disciplines, as well as consumer advocates. Through its award mechanisms and innovative approach, the BCRP plays a leading role in the breast cancer research community.

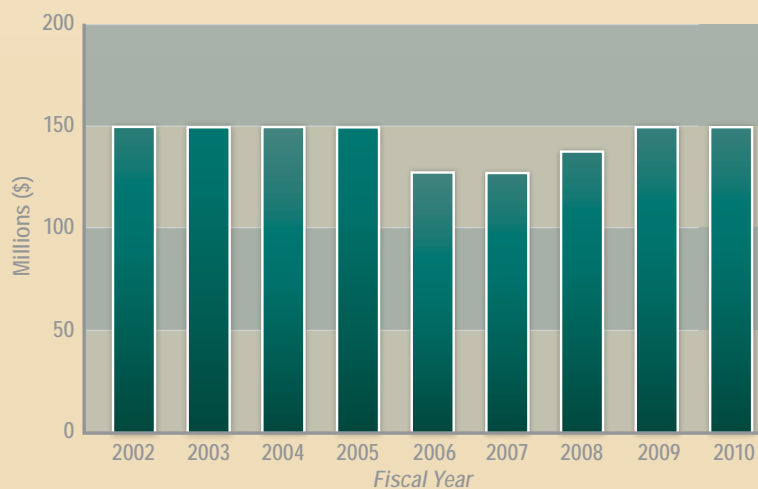
INVESTMENT GOALS

- * **Encourage innovation and stimulate creativity**
- * **Support research with high impact potential**
- * **Foster new directions and fill important gaps**
- * **Facilitate synergistic and multidisciplinary collaborations**
- * **Bring new investigators into the breast cancer field**
- * **Train investigators early in their careers**
- * **Encourage research in understudied topic areas**

The BCRP Funding Portfolio FY92–FY09



Recent BCRP Funding History



Funding for FY92–01 was \$1.2 billion.

Strategic Partnerships:

Consumer advocates and scientists working together to realize program goals

The BCRP is widely recognized as a model medical research program, and meaningful partnerships have been the foundation of the program's successes from the very beginning. Through this program, the integrated efforts of many dedicated individuals foster unique opportunities in breast cancer research. The two-tiered review process established by the BCRP brings together the expertise of scientists with the perspectives and experiences of breast cancer survivors (consumers). This innovative approach, which has since been adopted by other funding organizations, is a highly proven and effective way to evaluate research proposals for their potential to meet the program's goals.

Consumers and scientists serve critical roles in the BCRP:

- * As peer reviewers, they evaluate proposals for scientific and technical merits as well as the potential successful impact of the research.
- * As IP members, they make programmatic recommendations for the BCRP's vision, investment strategies, and funding selections intended to reflect the needs of the consumer and research communities.
- * As research participants, they partner on team-oriented award mechanisms, work together to focus research goals, and collaborate on the design and implementation of innovative research projects.

- * **Since FY93,** consumer advocates have participated in designing the BCRP's program priorities and funding opportunities
- * **Since FY93,** consumer advocates have participated as equal voting members in making funding recommendations during programmatic review
- * **Since FY95,** consumer advocates have participated as equal voting members in scientific peer review panels
- * To date, more than 2,000 scientists and consumers have contributed their expertise to the BCRP two-tier review process.



"The most important aspect of being part of the BCRP, for me, has been the interaction with consumer advocates. They have certainly affected the way that I think about breast cancer, but they have also impacted the way that I do science more generally. They are a constant reminder that our goal should be to impact people's lives."

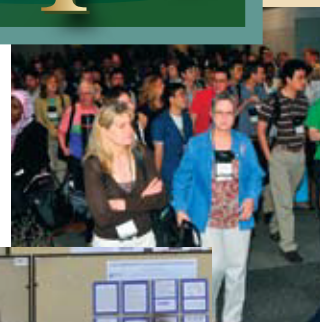
Greg Hannon
Cold Spring Harbor Laboratory
FY10 Integration Panel Chair

Era of Hope

The Era of Hope Meeting is a forum for presenting research studies funded by the BCRP. It is a unique opportunity for consumers and expert scientists from different fields and research areas to discuss unanswered questions, share ideas, identify promising directions in breast cancer research, and develop collaborative partnerships.

At the 2008 Era of Hope Meeting, more than 1,550 scientists, clinicians, and breast cancer survivors and advocates from more than 530 organizations came together to learn about advancements made since the BCRP's inception. More than 1,200 BCRP-funded research studies were spotlighted in symposia sessions and poster sessions while plenary sessions focused on emerging issues in breast cancer.

The next Era of Hope Meeting, which will be held on August 2–5, 2011, promises to be another valuable opportunity to hear about BCRP-funded research, as well as to ask, discuss, and learn about important questions for the future of breast cancer.



“It has been an honor and a privilege to represent the breast cancer community as a consumer reviewer for the DOD BCRP. The DOD BCRP is a unique collaboration and partnership between scientists and advocates, harnessing the best skills and insights of both to end breast cancer. I have had the opportunity to work with and learn from many brilliant scientists and advocates through peer review, programmatic review, and as a member of the Integration Panel. I can make a long-term, meaningful difference in the fight against breast cancer through this respected research program that challenges the status quo and encourages new ideas, innovation, and impact—all with a sense of urgency. We need new ideas and approaches if we expect to end this disease—the DOD BCRP gives me hope for a better future.”

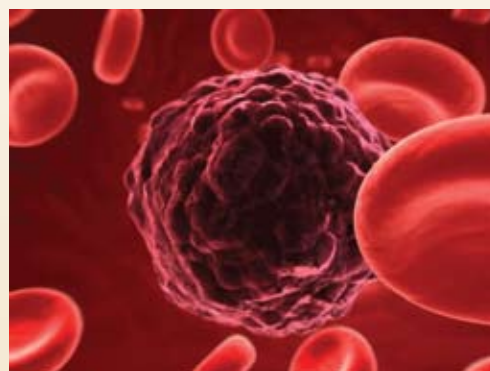


Pat Haugen
South Dakota Breast Cancer Advocacy
FY11 Integration Panel Chair

Investing in the next generation of innovators

The Role of Tumor Self-Seeding by Circulating Cancer Cells in Progression to Metastatic Breast Cancer **Mi Young Kim, Ph.D., Memorial Sloan-Kettering Cancer Center**

Understanding the molecular mechanisms of breast cancer progression is a necessary step toward developing effective treatments for this life-threatening disease. A Research Fellow at Memorial Sloan-Kettering Cancer Center, Dr. Mi Young Kim, received an FY06 BCRP Era of Hope Postdoctoral Award to study the mechanisms that regulate a novel process called “self-seeding”, i.e., the return of circulating tumor cells to the site of origin. Dr. Kim hypothesized that subpopulations of disseminated tumor cells return to the primary tumor site and that this process involves several functions from primary tumors as well as circulating tumor cells (CTCs).



Dr. Kim demonstrated that metastatic tumor cells have higher self-seeding abilities compared to poorly metastatic cells and that in vivo selected self-seeders (tumor cells with enriched self-seeding ability) exhibited a similar gene expression pattern found in bone, lung, and brain metastatic cell populations. Moreover, Dr. Kim identified two functions required for this process: (1) chemoattraction mediated by primary tumor of its own circulating progeny and (2) physical re-infiltration of primary tumor by CTCs in response to these attraction signals. Four genes were linked to the process: IL-6 and IL-8, secreted by a primary tumor, which attracted circulating tumor cells, and FSCN1 and MMP1, overexpressed by CTCs, which facilitated re-infiltration of CTCs into tumor. Finally, the self-seeding phenomenon was associated with accelerated tumor growth, enhanced angiogenesis, and increased recruitment of neutrophils and macrophages to the seeded areas of tumor, which may be regulated at least partially by the chemokine CXCL1, found to be overexpressed in self-seeders. These findings, recently published in the journal *Cell*, provide new insight on the mechanisms of self-seeding and potential targets for treatment.



“When I am on a DOD review panel, I make an effort to build relationships with the scientists, hoping to develop a cross-communication that can see new advocacy opportunities. I have already become involved as an active advocate on two major grant projects where the PI is someone I met on a panel.

The DOD Breast Cancer Research Program has been a center of my advocacy. I have grown in scientific understanding and have learned to communicate more effectively, which in turn has made me a stronger advocate.”

Amy Bonoff
Consumer Reviewer
SHARE

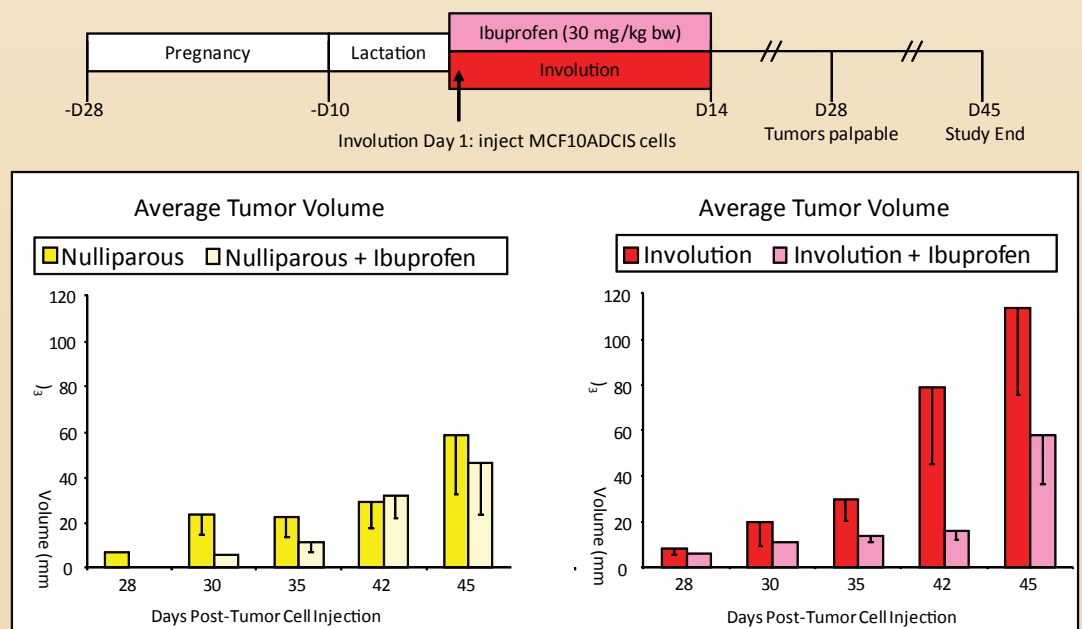


Preventing Progression of Postpartum Breast Cancer with NSAIDs Jenean O'Brien, University of Colorado Denver

In women, full-term pregnancy correlates with an increased risk of breast cancer for up to 10 years after birth. Further, patients diagnosed with breast cancer within 5 years postpartum have worse prognosis compared to women diagnosed during pregnancy. Tumor promotional changes that occur postpartum could account for the poor prognosis of these women. Following pregnancy, the breast remodels to its pre-pregnant state through a process called postpartum involution. During involution, the mammary gland displays wound healing and inflammatory characteristics associated with disease progression.

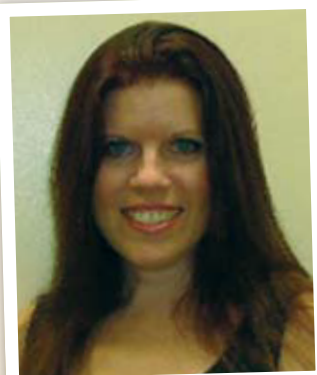
Jenean O'Brien received an FY07 BCRP Predoctoral Traineeship Award to study the inflammatory components of normal mammary gland involution, under the mentorship of Dr. Pepper Schedin. One of her goals was to test whether treatment with the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen or aspirin reduces this inflammatory response and, possibly, postpartum breast cancer progression.

To examine inflammation during involution, mammary tissue from rats was stained with antibodies to identify immune cells and cytokines. These studies revealed an increase in the type of macrophages normally associated with tumor promotion, providing the first direct evidence for macrophage activation during normal postpartum involution. Further, in a mouse model of postpartum breast cancer, ibuprofen treatment during involution decreased tumor volume and tumor cell infiltration of the lung compared to control-postpartum animals. Importantly, targeting involution with systemic ibuprofen or aspirin did not interrupt mammary epithelial cell regression that normally occurs during this period. These data suggest that similar to pathological wound healing and inflammatory tissue microenvironments, the physiological postpartum involution microenvironment in the breast promotes pre-existing cancerous lesions, and NSAIDs may be a useful treatment during involution to prevent progression.



Ibuprofen treatment targeted to involution reduces tumor burden to nulliparous levels. Top: time line of tumor xenograft study. Bottom: average tumor volume.

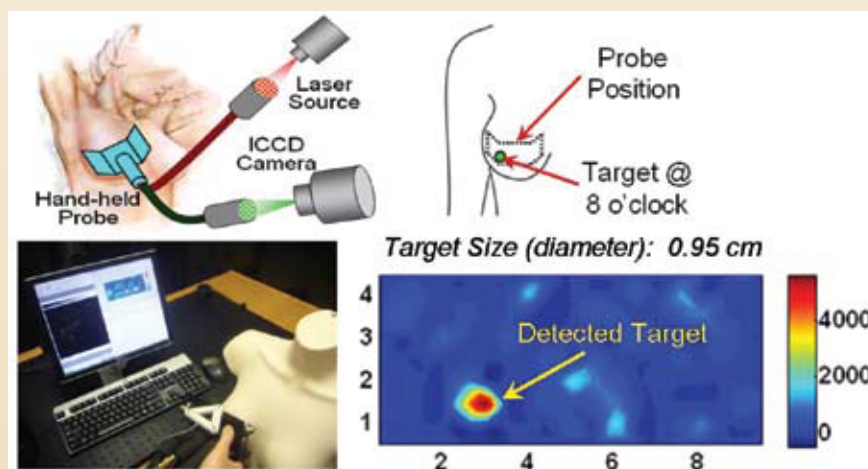
Program Highlights



A Novel Handheld Optical Imager for Breast Cancer Detection **Sarah Erickson, Florida International University**

Near-infrared (NIR) optical imaging is a noninvasive and nonionizing modality that is emerging as a powerful breast cancer diagnostic tool. In recent years, handheld-based optical imaging systems have been developed for the clinical setting, but these systems lack some of the capabilities of more traditional imagers. Sarah Erickson, recipient of an FY08 BCRP Predoctoral Traineeship Award, is currently testing a novel handheld optical imager to improve real-time surface imaging and three-dimensional tomographic analysis. If successful, this device could provide a valuable tool for diagnosing early-stage breast cancer.

In the past year, the imaging device has undergone several adjustments and performance assessments and was recently tested in human subjects. Fluorescent target(s) were noninvasively placed under the flap of the breast tissue (close to the chest wall) to simulate a breast tumor in healthy female volunteers. The device was able to detect successfully the fluorescent target through approximately 2.5 cm of breast tissue. Ms. Erickson and her mentor, Dr. Anuradha Godavarty, are currently conducting experiments to improve the real-time optical imaging capabilities of this device. Thus far, the results have suggested that by applying a unique multiple-scan technique, one could detect deeper targets. Ongoing studies are being performed to determine the deepest and smallest size target that can be detected using this technique. Currently, studies are being initiated to test the device on breast cancer patients.



Handheld optical imaging system developed at Florida International University for a safe and comfortable method of breast cancer diagnosis.



“It has been very meaningful to participate as a consumer reviewer for the DOD Breast Cancer Research Program because it has allowed me to provide a voice for those who have been affected by breast cancer to the scientific community. Having breast cancer survivors/advocates at the table fosters a program with goals shared by the researchers and the larger breast cancer community.”

Ilana Cohen
Consumer Reviewer
Breast Cancer Network of Strength



Development of Optical Coherence Tomography (OCT) Targeted Contrast Agents for Breast Cancer

Freddy T. Nguyen, University of Illinois at Urbana-Champaign

Freddy Nguyen, an M.D./Ph.D. student in Professor Stephen Boppart's Biophotonics Imaging Laboratory, was awarded an FY07 BCRP Predoctoral Traineeship Award to optimize the use of an innovative imaging technology, magnetomotive optical coherence tomography (MM-OCT), which can provide real-time microscopic analysis of tumor cells. Specifically, Mr. Nguyen's project is to develop and optimize protein microspheres as a multimodal contrast agent to be used in conjunction with MM-OCT.

Mr. Nguyen has focused on encapsulating iron oxide nanoparticles and fluorescent dyes into the inner cores of modified protein microspheres capable of specifically targeting tumor neovessels, which are the blood vessels that tumors form to support their rapid growth. Tumor neovessel specificity was achieved by coating the microspheres with an arginine-glycine-aspartate (RGD) peptide, which binds to the $\alpha v \beta 3$ integrin receptor on the surface of tumor neovessel endothelial cells. Preliminary studies confirmed that the microspheres preferentially bind to the tumor cells because they overexpress $\alpha v \beta 3$ integrins in vitro. The microspheres accumulated in the neovessels at the tumor sites when injected into tumor-bearing rats. Mr. Nguyen plans to further pursue the cancer-specific targeting of the protein microspheres as a potential diagnostic contrast agent as well as a therapeutic agent in the treatment of breast cancer.



Deciphering the function of MicroRNAs in Human Breast Cancer

Scott Valastyan, Massachusetts Institute of Technology

The multistep process of metastasis begins with the liberation of neoplastic cells from the primary tumor. This is followed by invasion of cancer cells into the blood vessels, survival within the bloodstream, tumor cells exiting the capillaries and, finally, entering distant organs and growing into secondary lesions. MicroRNAs (miRNAs) are RNAs that post-transcriptionally silence gene expression and function as both oncogenes and tumor suppressor genes. Half of all miRNA genes reside in regions perturbed during tumorigenesis within a variety of tumor types, including breast cancer. Under the mentorship of

Dr. Robert Weinberg, Scott Valastyan discovered a miRNA, miR-31, whose levels are significantly diminished in metastatic breast cancer cells compared to normal breast epithelial cells and non-metastatic breast cancer cells. Awarded a FY08 Predoctoral Traineeship Award, Mr. Valastyan will decipher the function of this miRNA, how its expression is regulated, and how it is relevant to disease progression in breast cancer patients.

Mr. Valastyan found that miR-31 correlates inversely with metastatic recurrence in breast cancer patients and impedes metastasis in aggressive breast tumor cells grown in mice. When miR-31 was inhibited, nonaggressive breast cancer cells began to metastasize, which was achieved by pleiotropic modulation of a cohort of metastasis-promoting genes, including RhoA, integrin $\alpha 5$, and radixin. miR-31 had no effect on primary tumor development, but specifically targeted the multi-step process of metastasis. Conversely, overexpressing miR-31 in aggressive breast tumor cells suppressed their ability to metastasize. These results indicate that loss of a single gene product, miR-31, can block multiple steps of the invasion-metastasis cascade. Moreover, as a potent suppressor of breast cancer metastasis, miR-31 could one day represent a clinically useful prognostic marker or therapeutic target.

Pursuing innovative ideas and new paradigms

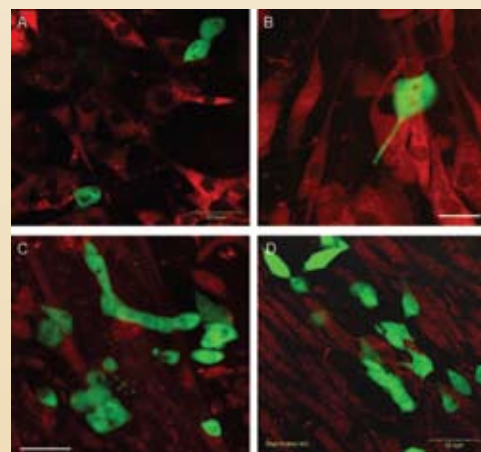


A New in Vitro Model of Breast Cancer Metastasis to Bone **Andrea Mastro, Ph.D., Pennsylvania State University**

Breast cancer metastases to bone frequently results in osteolytic lesions with concomitant hypercalcemia, pain, spinal cord compression, and fractures. Bone metastases are also difficult to treat; the 5-year cure rate of these breast cancer patients is only 16%. Current treatments are directed at inhibiting the function of osteoclasts, the bone cells responsible for resorption. Relatively little research, however, has been conducted examining the role of osteoblasts in bone degradation. Dr. Andrea Mastro, recipient of an FY05 BCRP Idea Award, previously found that in the presence of breast cancer cells, osteoblasts secrete

inflammatory cytokines. She believes that osteoblasts are a major contributor to bone lesions associated with breast cancer metastases due to their inability to rebuild the bone resorbed by osteoclasts. In this study, Dr. Mastro, together with Dr. Erwin Vogler, a biomaterials scientist and bioengineer, proposed to study the interactions of metastatic breast cancer cells with bone by developing a novel bioreactor system to form synthetic, three-dimensional bone tissue and to test drugs affecting osteoblast function in a breast cancer cell system.

In long-term cell cultures, the osteoblasts differentiated into osteocytes and produced bone depositions. This work provided the first evidence of osteocyte differentiation in tissue culture. Using this bioreactor system, Dr. Mastro grew human metastatic breast cancer cells in co-cultures with osteoblasts. Interestingly, the metastatic cancer cells down-regulated osteoblast differentiation proteins but increased inflammatory cytokines. The cancer cells attached to the osteoblasts in co-culture and penetrated the osteoblast layer. Furthermore, the osteoblasts changed morphology to spindle shape, and the cancer cells aligned in single-cell files with the osteoblasts. This cancer cell behavior is seen in vivo but not in standard cell culture conditions. Dr. Mastro also examined the effects of zoledronic acid (ZOL), a bisphosphonate that prevents the loss of bone mass, in co-cultures with breast cancer cells and osteoblasts. She found that in the presence of ZOL the metastatic breast cancer cells formed smaller colonies and failed to form projections or penetrate the extracellular matrix as seen in cultures without ZOL. This award was very successful in developing a model system to study in vivo bone metastatic colonization and in identifying osteoblasts as an important therapeutic target.



Co-culture of MDA-MB-231GFP with MC3T3-E1 osteoblasts in the bioreactor. MC3T3-E1 were cultured for 5 months in the compartmentalized bioreactor prior to the addition of MDA-MB-231 metastatic breast cancer cells. The osteoblasts were visualized by Cell Tracker Orange™ vital stain. The cultures were monitored by confocal microscopy (day 1 for A; day 3 for B-D). A. Cancer cells attached to the osteoblasts. B. A cancer cell with a pseudopod penetrated the osteoblast layers. C. Cancer cells formed into single cell files. D. Osteoblasts changed morphology to spindle shaped and the cancer cells aligned with them. Magnification bars represent 50 microns.

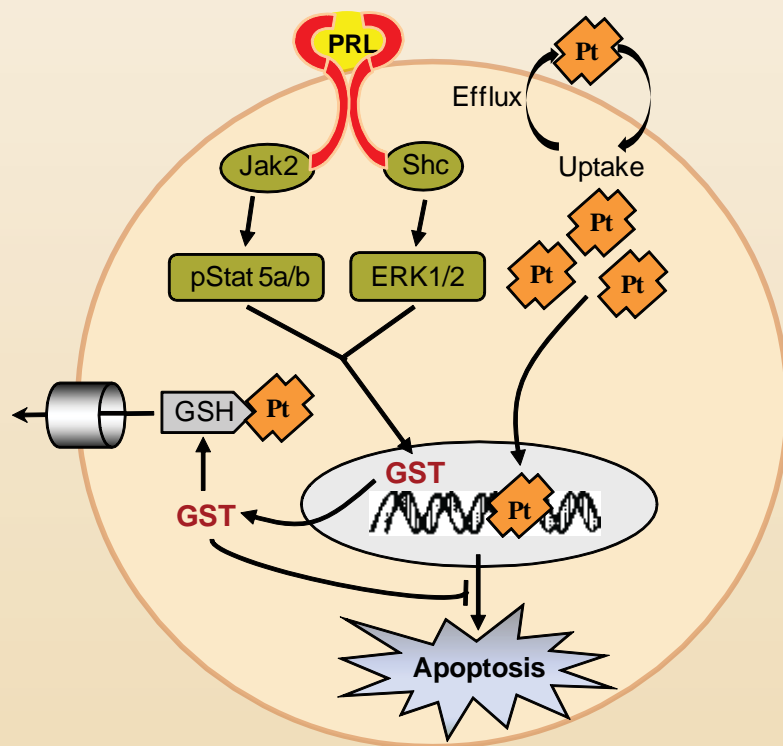


Understanding Cisplatin Chemoresistance

Nira Ben-Jonathan, Ph.D., University of Cincinnati

Chemoresistance to cisplatin, a platinum-based chemotherapeutic drug used to treat breast cancer, can be caused by a number of factors, including the detoxification enzyme glutathione-S-transferase (GST). The role of hormones in chemoresistance has not been widely studied, despite breast cancer being hormone-sensitive. Prolactin, a protein hormone expressed in breast tissue and breast cancer cell lines, is known to function as a survival factor in malignant and nonmalignant cells. Dr. Nira Ben-Jonathan, an FY05 BCRP Idea Award recipient, hypothesized that prolactin antagonizes apoptosis by anticancer drugs

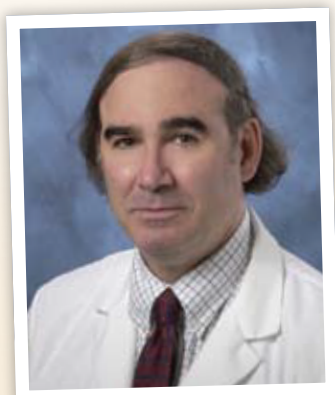
and may play a role in chemoresistance. She found that the actions of prolactin as a survival factor can be mediated through several signaling pathways, but its protective effect involves the Jak-Stat and MAPK pathways. In cisplatin-treated cells, prolactin reduced the amount of platinum bound to DNA by 50%. It also antagonized cisplatin cytotoxicity through GST, increasing the detoxification enzyme's activity while reducing the drug's ability to enter the cell nucleus. Based on her research findings, Dr. Ben-Jonathan conceptualized the mechanism through which prolactin antagonizes cisplatin-induced apoptosis. Her results led to the first demonstration of a natural hormone conferring chemoresistance in breast cancer cells.



"I didn't just want to survive my breast cancer. I wanted to survive and thrive. Women everywhere battling breast cancer should have that chance, and the research advanced by the DOD Breast Cancer Research Program offers that promise. Participating in the BCRP peer review was an honor and an incredible learning experience."

Rachel Howzell Hall
Consumer Reviewer
UCLA Breast Center



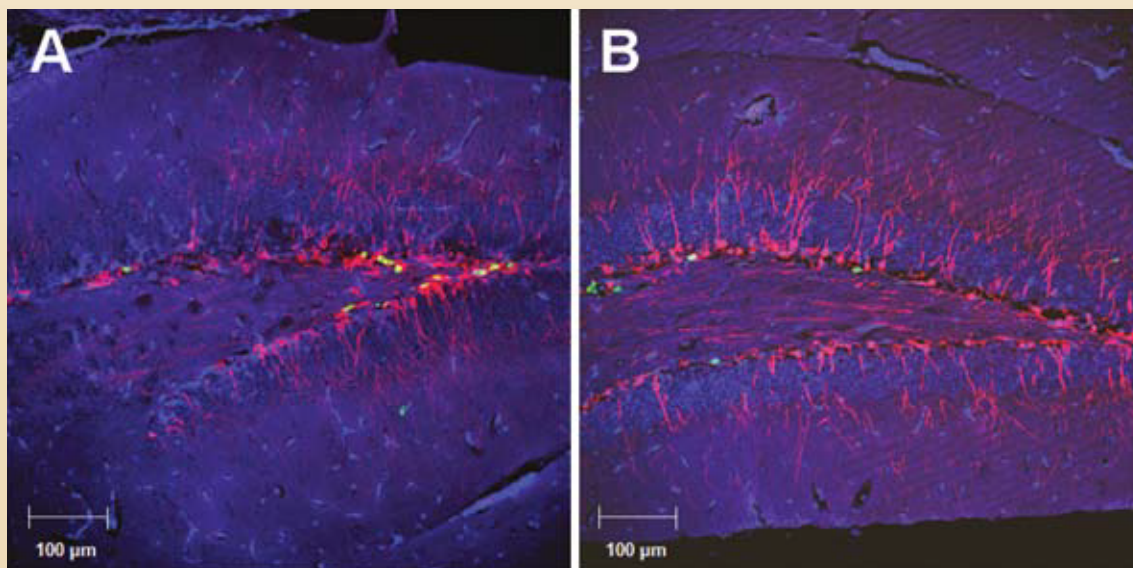


Unlocking the Key to Chemobrain

Robert Pechnick, Ph.D., Cedars-Sinai Medical Center

Breast cancer patients who have received adjuvant treatment for breast cancer often complain of cognitive impairments, or chemobrain. Symptoms of chemobrain can include frequent memory lapses, difficulty concentrating, inability to remember details, inability to multitask, and trouble remembering common words or names. Since medical advances have resulted in increased long-term survival, it has become increasingly important to find effective chemotherapeutics with fewer side effects. In FY07, Dr. Robert Pechnick received a BCRP Concept Award to develop and utilize a mouse model to study the effects of chemotherapeutic drugs on cognitive function. Dr. Pechnick is studying the hippocampus, where neural stem cells and progenitors proliferate and differentiate into neurons, and a phenomenon called neurogenesis, which he believes is prevented by chemotherapeutics and could lead to chemobrain.

Laboratory mice were administered doses of the chemotherapeutic drugs cyclophosphamide, 5-fluorouracil, and methotrexate. Behavioral testing was carried out and hippocampal neurogenesis was assessed. Methotrexate caused deficits in performance in the spontaneous alternation task and the Barnes maze, two procedures where spatial and working memory are measured. Methotrexate also reduced hippocampal neurogenesis. These data suggest that certain chemotherapeutic agents can indeed produce cognitive impairments by disrupting hippocampal neurogenesis.



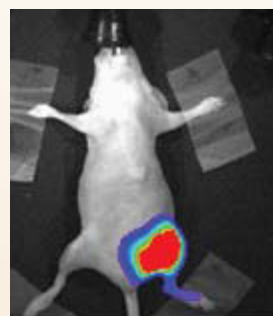
Sections of the hippocampus in saline- (A) and methotrexate-treated (B) mice. Dividing cells are labeled green, whereas immature neurons are labeled red. Treatment with methotrexate reduced the number of proliferating neurons, and showing that this chemotherapeutic drug disrupts hippocampal neurogenesis.



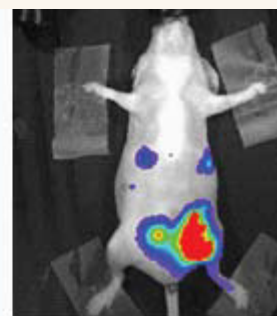
Finding the Upstream Regulator of Metastases
Erica Sloan, Ph.D.,
University of California,
Los Angeles

Recent studies have indicated that chronic stress can promote tumor metastasis; however, the cellular mechanisms are unknown. Dr. Erica Sloan has inves-

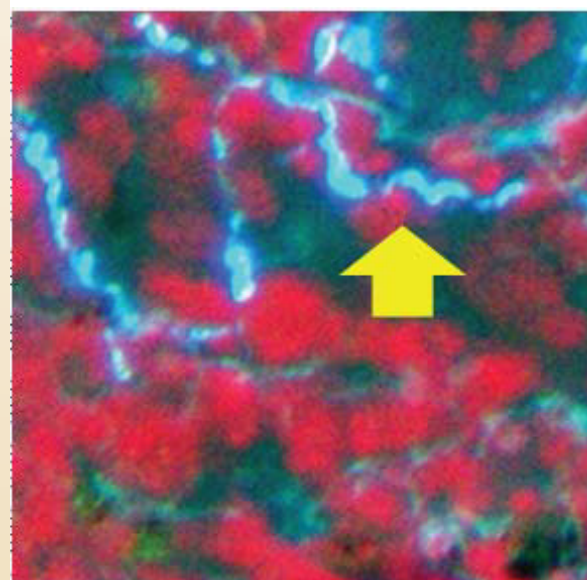
tigated stress-induced sympathetic nervous system activity as a host factor that might regulate the metastatic tumor microenvironment. With funding from an FY09 BCRP Concept Award, Dr. Sloan used advanced imaging to track the impact of stress-induced neural activation on cancer progression in a mouse model of human breast cancer. Dr. Sloan's findings revealed that chronic stress significantly increased metastasis to lymph nodes and lung. The effect of stress could be prevented by treating mice with beta-blockers. These findings suggest that neural pathways play a key role in mediating breast cancer metastasis and may be a new target for antimetastatic therapies



Control



Stress



Top: Black and white images of mice showing the location of tumor cells with red indicating the highest density of tumor cells at the primary tumor (4th mammary fat pad) and purple/blue showing the lowest density of tumor cells.

Bottom: A high magnification photograph taken within a lymph node showing immune cells (red) in close proximity to SNS nerve fibers containing stress neurotransmitters (blue-white).



"After participating in BCRP peer review, I am confident that only the best research is getting funded. Each proposal is thoroughly reviewed not only by experts in the science fields, but also by consumers who consider how the research would affect quality of life for breast cancer survivors."

Mary Justice
Consumer Reviewer
Breast Cancer Alliance of Greater Cincinnati

Program Highlights



Monitoring Breast Cancer Response to Neoadjuvant Therapy Flemming Forsberg, Ph.D., Thomas Jefferson University

Neoadjuvant chemotherapy alone or in combination with endocrine therapy is commonly used to treat locally advanced breast cancer (LABC) and operable palpable breast cancers. It has been hypothesized that breast cancers with high interstitial fluid pressure (IFP) respond poorly to chemotherapy because of poor drug delivery. Dr. Flemming Forsberg received an FY07 BCRP Idea Award to develop a method to noninvasively quantify the IFP in breast cancers and determine if IFP can be used as a quantitative surrogate endpoint for assessing response to chemotherapy.

Dr. Forsberg is applying a noninvasive technique called SHAPE, or subharmonic-aided pressure estimation, which utilizes ultrasound contrast microbubbles (gas bubbles that are encapsulated and used as a contrast agent) to compare hydrostatic pressure in relation to the subharmonic amplitude of the scattered signal. Dr. Forsberg evaluated SHAPE's effectiveness by testing two different contrast agents, Definity and Sonazoid, to measure IFP in vitro. Both Definity and Sonazoid showed an inverse linear relationship between the change in subharmonic amplitude and hydrostatic pressure. Although both contrast agents demonstrated sensitivity, Definity was more responsive than Sonazoid. Dr. Forsberg believes that these results indicate that using SHAPE for noninvasive evaluation of the IFP in breast lesions is feasible and will be further studied in a rat model of breast cancer to monitor treatment response.



"It is so inspiring to see the caliber of the scientists and physician researchers who are involved in breast cancer research and the type of research that is being conducted to help eradicate this disease. I hope to one day see that a panel I served on helped find research that led to a major breakthrough for breast cancer."

Joan Isman
Consumer Reviewer
Ann's Place, the Home of I Can



Delivering Therapeutics to Her-2 Neu Positive Breast Cancers
Rita Serda, Ph.D., University of Texas Health Science Center at Houston

Targeted therapies require not only the development of the therapeutic agent, but also the vehicle to deliver it to the tumor site. Dr. Rita Serda, an FY06 BCRP Multidisciplinary Postdoctoral Award recipient, is developing a first-stage porous silicon particle that can deliver second-stage iron oxide nanoparticles to human breast cancer cells. The nanoparticles will specifically target the elevated angiogenic and cell adhesion molecules expressed on tumor-associated endothelial cells. Through in vitro experiments, Dr. Serda found that endothelial cell morphology, viability, and mitosis were unaffected by the nanoparticle treatment, demonstrating that the nanoparticles were safe and not proinflammatory. She also showed that inflammatory cytokines (e.g., TNF-alpha) enhanced nanoparticle uptake by endothelial cells. When animals inoculated with 4T1 breast cancer tumors were treated with the nanoparticle-based contrast agent, magnetic resonance imaging revealed negative contrast in the tumor, indicating the presence of the nanoparticle. Further testing will be done to enhance tumor-specific delivery of nanoparticles for the delivery of imaging agents and therapeutic drugs.



Mathematical Modeling of Rho Function in Breast Cancer: Correlation with Spectroscopic and Biochemical Experiments
Alejandra Ventura, Ph.D., University of Michigan

It has been hypothesized that a number of gene-related abnormalities signal the development of breast cancer, or the progression to more aggressive types such as Inflammatory Breast Cancer (IBC). Dr. Alejandra Ventura, recipient of an FY05 BCRP Multidisciplinary Postdoctoral Award, is studying the temporal dynamics of the RhoC protein, which is a known oncogene that plays a critical role in IBC. Dr. Ventura is testing lysophosphatidic acid (LPA), an activator of the RhoC pathway, which can simulate the natural IBC tumor microenvironment, to develop a novel dual mathematical-experimental approach to examine this cycle and its probable deregulation in cancer cells. This dual mathematical/experimental approach will provide the theoretical framework to allow for quantitative predictions of the effects of drugs targeted against RhoC.

Dr. Ventura was able to develop a mathematical model to exemplify the behavior of both active and total RhoC protein levels, helping to correlate the dynamic response of activation and expression of RhoC. Experiments showed that in some cases RhoC protein levels were unchanged after LPA stimulation, which contends a possible intrinsic property of RhoC that is distinctive of invasive metastatic breast cancers. Dr. Ventura also demonstrated in her experiments that IBC is a unique form of breast cancer due to the overexpression of RhoC, and this particular activation pattern of RhoC is likely only found in IBC showing a distinct inflammatory and metastatic phenotype. Dr. Ventura has begun to utilize this type of mathematical approach in analyzing intracellular signal transduction pathways.

Touching lives and accelerating translation

Eradicating Brain Metastases Patricia Steeg, Ph.D., Center for Cancer Research, National Cancer Institute

Brain metastases are increasing in incidence and now occur in an estimated one-third of metastatic breast cancer patients with either Her-2 positive tumors or triple-negative tumors. Only 20% of the patients diagnosed with brain metastases are expected to live beyond 1 year after diagnosis. Treatments include radi-

ation, steroids, and surgery; unfortunately, these interventions are not curative and often result in significant quality of life complications. In FY05, Dr. Patricia Steeg was awarded a BCRP Center of Excellence (COE) Award to form the first community of consumers and investigators to address the issues associated with breast cancer brain metastases. Since the award's inception, Dr. Steeg and 16 other investigators have conducted considerable translational and clinical research. The group assembled human surgical brain metastasis specimens, conducted molecular analyses to identify functional pathways, and is preclinically testing brain-permeable therapeutics. Several brain-permeable drugs have been preclinically validated to prevent brain metastasis formation including lapatinib and pazopanib for Her-2 positive brain metastases, and vorinostat (suberoylanilide hydroxamic acid or SAHA) for triple-negative tumors, the latter in combination with radiation therapy. Currently, a Phase II trial is being conducted with vorinostat (Zolinza™) and either stereotactic or whole brain radiotherapy.

The website www.BrainMetsBC.org was launched for posting interviews with oncologists and members of the COE, updates on treatment information, patient experience letters, clinical trial information, and publication lists. To date, the website has had nearly 80,000 visitors, and the COE plans on launching a Spanish version in the upcoming months.

One goal of the COE award mechanism is to partner clinicians and scientists with consumer advocates who fully participate in all aspects of the award. In 2009, Dr. Steeg's COE group was joined by Ms. Lilla Romeo, an accomplished speaker, trained advocate, and compelling voice for metastatic breast cancer patients. Ms. Romeo published a welcome letter on the website, sharing both her story and her relationship with the COE group. She continued to be an active presence and advocate until her battle with breast cancer ended in June 2010.





Breaking Down the Disparities in Breast Cancer Treatment Among Races and Ethnicities

Scarlett Lin Gomez, Ph.D., Cancer Prevention Institute of California

It has been shown that the burden of breast cancer is unevenly distributed across various ethnic groups, particularly when it comes to diagnosis and treatment of the disease. Dr. Scarlett Lin Gomez, recipient of an FY06 BCRP Idea Award, and her team at the Cancer Prevention Institute of California hypothesize that institutionalized discrimination in the social and physical environments of minority neighborhoods leads to the racial and ethnic disparities seen in breast cancer out-

comes. Based on this hypothesis, the researchers launched an innovative epidemiologic study in this sparsely researched area of public health.

The research team designed a questionnaire to ascertain the impact of individual- and institutional-level discrimination on diagnosis and treatment. The questionnaire includes an assessment for evaluating medical and general discrimination across multiple domains, as well as questions on stress, coping, social support and social networks, social burden, patient-provider communication, culture factors and beliefs, culture health capital, socio-demographics, treatment and comorbidity, quality of life, neighborhood environment, clinical trial participation, immigrant and children of immigrant stress, and social desirability bias. Preliminary data suggest that breast cancer survivors, notably racial/ethnic minorities, experience more negative aspects in the realm of social support. The data reflect that women from racial/ethnic minorities have limited support networks and during the emotionally stressful period after breast cancer diagnosis and during treatment often develop interpersonal conflicts, including marital issues and negative social interactions with family, friends, and co-workers. Women also experience discrimination in the medical community, specifically unfair treatment, lack of treatment options, or lack of an explanation of treatment options, all suggesting poor standard of care. As more interviews are conducted, Dr. Gomez believes a more accurate definition of the environmental factors surrounding racial/ethnic disparities in breast cancer will emerge.



“As a younger woman diagnosed with breast cancer, the DOD BCRP provides me with an opportunity to make sure research in breast cancer is reaching the whole spectrum of individuals diagnosed. I love that my voice can help lead to finding a cure so that the next generation may have a chance at never having to deal with this disease.”

**Kathleen Werner
Consumer Reviewer
Young Survival Coalition**



Program Highlights



Scanning the Genome in African American Women **Christopher Haiman, Sc.D., University of Southern California**

Genes and the environment both play important roles in the development of breast cancer. Studying genetic risk factors has been arduous and only mildly successful due to the complexity of the genome and the large number of genetic variants that must be analyzed. Genome-wide association studies have been performed on women of European descent, and these studies have successfully identified several common risk alleles for breast cancer. However, Dr. Christopher Haiman believes these findings may not explain genetic risk for the disease in all populations. Using his FY07 BCRP Era of Hope Scholar Award,

Dr. Haiman is performing the first genome-wide association study of breast cancer among African American women.

In the first 2 years of the study, Dr. Haiman has genotyped 5,984 samples and analyzed 1,043,036 single nucleotide polymorphisms (SNPs) that include ancestry informative SNPs used to differentiate the degree of African and European ancestry of each sample. He was able to demonstrate that the majority of the susceptibility loci that were identified in European and Chinese populations are not strong markers of risk among African Americans. The most significant associations from the scan are currently being examined in a number of additional studies of African ancestry associations. As these data are analyzed, Dr. Haiman believes this information will lead to a better understanding of the susceptibility of breast cancer in African Americans and may possibly shape personalized prevention and therapeutics.



“Initially, I joined the CDMRP BCRP review process because I thought it might help me become a more educated patient and a much better advocate for myself and my own treatment. It did just that, but what I also learned over time was how to be an advocate for others. I’ve become a patient advocate, a breast cancer navigator, and an advocate of clinical trials and for underserved populations. I’m certain that developing breast cancer in my early 20’s was all part of some divine plan that led me to serve as a consumer reviewer for the CDMRP. The knowledge and information I’ve gained from this program have been the tools by which I spread hope and faith to others fighting this disease. I’ll continue to serve as a consumer reviewer for the CDMRP as long as the guidelines say I can, or until we find a cure... whichever comes first.”

Jocelyn Whitfield Banks
Consumer Reviewer
Pink Ribbon Girls



Identifying the Next Generation of Breast Cancer Susceptibility Alleles

Nazneen Rahman, M.D., Ph.D., Institute of Cancer Research, London

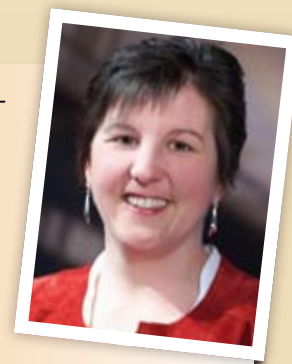
In the last decade, much progress has been made toward discovering the genetic factors predisposing to breast cancer. Mutations in BRCA1, BRCA2, and TP53 are rare, but they account for a greater than 10-fold increased risk of breast cancer. Mutations in CHEK2, ATM, PALB2, and BRIP1 are also rare but confer an approximately twofold increased risk. Collectively, these genetic mutations account for 20% to 30% of the familial risk of breast cancer, which suggests that a large number of genetic factors have yet to be identified. Dr. Nazneen Rahman, recipient of an FY04 BCRP Era of Hope Scholar Award, proposed to perform a genome-wide familial case versus control analysis of single nucleotide polymorphisms (SNPs) to identify those that are associated with breast cancer.

Analysis of 582,866 SNPs in 3,659 breast cancer cases with a family history of the disease and 4,897 controls identified five novel susceptibility loci on chromosomes 9, 10, and 11. These associations were then confirmed in 12,576 further cases of breast cancer and 12,223 controls.

One locus, containing the SNP rs1011970 on chromosome 9, includes the genes CDKN2A and CDKN2B. These genes encode cyclin-dependent kinase inhibitors and are frequently deleted and mutated in various tumors. The loci containing the SNPs rs2380205, rs10995190, and rs704010 on chromosome 10 lie near the genes ANKRD16/FBXO18, ZNF365, and ZMIZ1, respectively. On chromosome 11, rs614367 showed an increased risk of breast cancer with increased age; the association was also stronger in those with a positive family history. All loci showed a strong relationship with estrogen receptor-positive disease. However, for rs2380205 and rs704010 there is evidence of an equivalent effect in estrogen receptor-negative cases. This study suggests that the remaining unexplained genetic risk of breast cancer is likely due to a large number of further common variants.

“As a young metastatic breast cancer survivor, it is very rewarding to participate in the DOD BCRP and to be able to represent the community of survivors that is way too large. I contribute with hopes that we will soon find a cure and prevent future generations from having to experience breast cancer.”

Lee Halarewicz
Consumer Reviewer
Susan G. Komen for the Cure



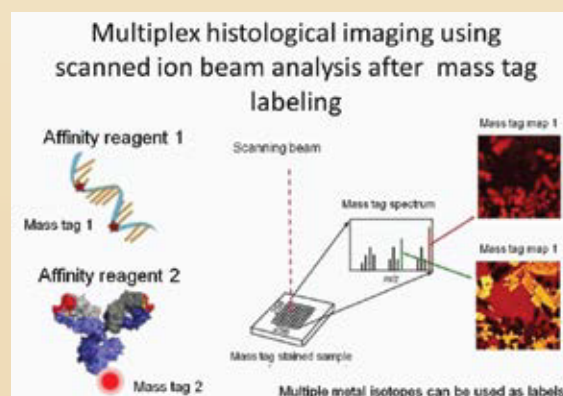
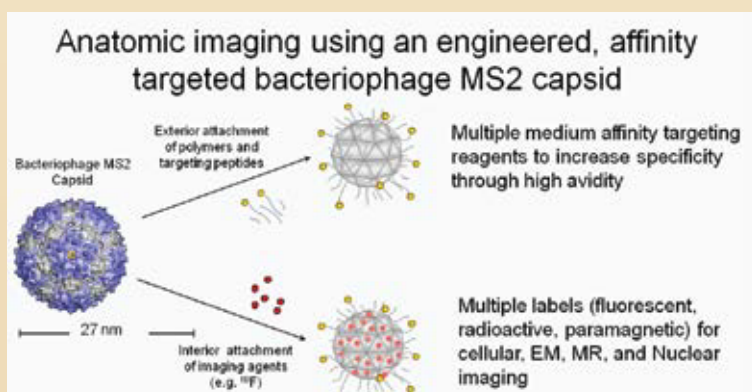


Early Detection of Metastasis-Prone Breast Cancers Joe Gray, Ph.D., Lawrence Berkeley National Laboratory

Improved breast cancer screening approaches are important since current procedures sometimes do not identify metastasis-prone cancers before they have spread beyond the site of the original cancer. Dr. Joe Gray, recipient of an FY06 BCRP Innovator Award, and his colleagues at Lawrence Berkeley National Laboratory, UC Berkeley, and UC San Francisco are focusing both on state-of-the-art anatomic imaging strategies that will better detect and locate metastasis-prone cancer precursor lesions, and on developing new tissue imaging procedures that will allow sensitive detection of rare cells that have spread beyond the site.

The tissue imaging procedures also will allow assessment of the activity of pathways targeted by new therapeutic strategies to better select patients most likely to respond to these agents. This type of information could prove valuable in improving management of metastasis-prone cancers for high-risk patients for whom early detection and more effective treatments are critical.

The anatomic imaging strategies developed by Dr Gray's team are based on the use of viral capsids and filamentous phage labeled with contrast reagents for MRI, optical and/or PET scans, and targeted to specific molecules that are present on the surfaces of metastasis-prone cancers. These imaging procedures could potentially detect lesions at a much earlier stage than traditional mammographic imaging techniques. Dr. Gray's team also is developing time-of-flight secondary ion mass spectrometry (ToF-SIMS) imaging of tissue sections stained with metal isotope-labeled antibodies against proteins found in metastasis-prone cancers. This particular method is unique in that it may lead to procedures that quantify multiple proteins associated with metastasis-prone cancer. This could lead to improved detection of rare disseminated cancer cells and allow identification of cancers that will respond well to specific pathway-targeted therapies. Together, the techniques under development by Dr Gray and his team may one day ensure better and earlier detection and treatment of metastasis-prone cancers.



Conceptual approaches to detection of metastasis-prone breast cancers before they have metastasized using new anatomical and histological imaging techniques.

Alan Wells and Linda Griffith
**"Escape from Tumor Cell
Dormancy"**
**FY09 Idea
Expansion Award**

Seth Field "A
New Path to
Breast Cancer
Therapy"
FY09 Era of
Hope Scholar
Award

Dmitri Simberg
**"Engineered
Erythrocytes for
Prevention of
Dissemination
of Metastatic
Breast Cancer"**
FY09 Idea Award

Guangwei Du
"Identification of
Druggable Proteins
Regulating Receptor
Recycling in Breast
Cancer Cells"
FY09 Concept Award

Rakesh Jain "Strategies for
Personalized Treatment of
Metastatic Breast Cancer:
Vascular Normalization and
Sensitization"
FY09 Innovator Award

Liviu Mirica
"Specific Inhibitors
of Histone
Demethylases:
Novel Chemical
Agents for Breast
Cancer Therapy"
FY09 Concept Award

Wei-Zen Wei "Systemic and
Local Vaccination against
Breast Cancer with Minimum
Autoimmune Sequelae"
FY09 Idea Expansion Award

**Lianjie Huang,
Donald Ingber,
Michael Williamson**
**"Breast Cancer:
Catch It with
Ultrasound"**
**FY09 Multi-Team
Award**

Jerrold Olefsky
"Role of Inflammation
and Insulin Resistance
in Mouse Models of
Breast Cancer"
FY09 Idea Award

Wei Chen
**"Nanoparticle
Self-Lighting
Photodynamic
Therapy for Breast
Cancer Treatment"**
FY09 Idea Award

Pilar Blancafort
and Brian Strahl
"Rewriting the
Histone Code of
Breast Cancer
Stem Cells"
FY09 Idea Award

Kelley Madden
"Sympathetic Nerves
in Breast Cancer:
Angiogenesis and
Antiangiogenic Therapy"
FY09 Idea Award

**Elaine Hardman and
Philippe Georgel**
**"Maternal Consumption
of Omega 3 Fatty Acids
to Reduce Breast Cancer
Risk in Offspring"**
**FY09 Idea
Expansion Award**

Richard Santen,
"Hormonally
Induced Purge
of Secondarily
Resistant Breast
Cancer Cells"
FY09 Idea Award

**Lisa McCawley "Breast
Cancer Tissue Bioreactor
for Direct Interrogation and
Observation of Response
to Antitumor Therapies"**
FY09 Idea Award

Sowing the Seeds for Innovative, High-Impact Research

IN THE PIPELINE

Proximity camera – Dr. Sarah Blair

Funded the development and clinical testing of a proximity camera for real-time intraoperative cancer cell detection at tumor margins during partial mastectomy.

Novel hyaluronic acid (HA) drugs – Dr. Glenn Prestwich

Funded research and development of novel HA-conjugated drugs that target HA receptors on cancer cells for enhanced delivery of anti-cancer agents.

Homing peptides – Dr. Erkki Ruoslahti

Funded the identification of homing peptides that specifically home to breast tumors and have the potential to deliver drugs or treatments to tumors with higher efficacy and reduced side effects.

Her-2 Bi-armed activated T cells (HB-ATC) –

Dr. Lawrence Lum

Supported a Concept Award that led to the discovery that HB-ATC induce memory antigen-specific cytotoxic T lymphocytes directed at Her-2/neu. HB-ATC are currently entering Phase II clinical trials.

Curcumin analog EF24 – Dr. Mamoru Shoji

Funded the discovery of EF24, a novel curcumin analog that specifically targets tumor blood vessels.

Ligand-transformed alpha-fetoprotein peptide (AFPep) – Dr. James Bennett and Dr. Thomas Andersen

Supported the development of AFPep and translational research on its potential efficacy as a treatment of estrogen receptor-positive breast cancer.

Molecular breast imaging – Dr. Carrie Hruska

Supporting clinical studies to determine if molecular breast imaging has comparable sensitivity and specificity to magnetic resonance imaging and may be a more cost-effective alternative for women who have dense breast tissue and increased cancer risk. A clinical trial is currently in progress.

Optical spectroscopy – Dr. Nimmi Ramanujam

Supported the development and clinical testing of optical spectroscopy to better identify tumor margins during surgery.

Computed mammoTomography (CmT) –

Dr. Randolph McKinley and Dr. Martin Tornai

Supported the development of CmT to overcome the limitations of conventional mammography and improve imaging for earlier detection and diagnosis.

HER-2/neu-derived peptide vaccine, E75 –

Dr. Constantin Ioannides

Supported characterization of immunodominant epitopes in breast cancer that led to the development of the E75 vaccine, an immunogenic peptide-based vaccine that is entering Phase III clinical trials.

Ductal Lavage – Dr. Susan Love

Supported the development of a minimally invasive diagnostic procedure for detecting precancerous and cancerous breast cells in fluid from the breast ducts.

MAKING AN IMPACT

Herceptin® – Dr. Dennis Slamon

Provided early funding for research leading to the development of monoclonal antibodies against the HER-2/neu receptor, now known as trastuzumab or Herceptin.

Sentinel lymph node biopsy – Dr. Lorraine Tafra and Dr. Kathryn Verbanac

Supported a clinical trial testing the validity and accuracy of sentinel lymph node biopsy, the current standard of care for disease staging.

Skp 2 expression – Dr. Michele Pagano

Supported the establishment of Skp2 as an oncogene that has high expression in human breast tumors correlating with destabilization of p27 and with poor survival. Immunohistochemical analysis of p27 and Skp2 expression levels is now common practice in clinical laboratories of pathology.

shRNA libraries – Dr. Gregory Hannon and Dr. Stephen Elledge

Supported the development of gene silencing and genetic screening strategies to identify new potential therapeutic targets. These shRNA libraries are available to the scientific community.

PTEN tumor suppressor gene – Dr. Michael Wigler

Funded the discovery of a homozygously deleted locus on chromosome 10, which identified the PTEN tumor suppressor gene mutation that is found in many breast cancers and other cancer types.

Margaret Dyson Family Risk Assessment Program – Dr. Mary B. Daly

Supported the establishment of a high-risk breast cancer registry to gather genetic and environmental risk information about women with familial breast cancer. This registry evolved into the Margaret Dyson Family Risk Assessment Program that now serves a large urban area with a range of risk assessment, screening, and preventive services.

Carolina Mammography Registry (CMR) – Dr. Bonnie Yankaskas

Funded the infrastructure development for this population-based mammography registry as a resource for studying community-based screening. The CMR is now a member site for the NCI Breast Cancer Surveillance Consortium.

OncoVue – Dr. Eldon Jupe

Supported early work on risk associations between BRCA1, BRCA2, prohibitin T allele, and breast cancer. These studies formed the foundation for a new breast cancer risk assessment test called OncoVue that has been through an FDA investigational device exemption (IDE) study and is now commercially available.

Adjuvant Tamoxifen Longer Against Shorter (ATLAS) Clinical Trial – Dr. Richard Peto

Supported initiation of the Phase III clinical trial, ATLAS, the largest breast cancer treatment trial ever undertaken. It examined the optimal duration of adjuvant tamoxifen in early-stage breast cancer.

Stereoscopic mammography – Dr. David Getty

Funded a Phase III clinical trial demonstrating that stereo mammography reduces false positive reports and is more accurate than standard mammography in detecting true breast cancer lesions.

Three-dimensional (3D) culture systems – Dr. Mina Bissell

Supported the development of a 3D culture system and assay to study breast cancer heterogeneity and the role of the tissue microenvironment in breast cancer development.

Disparity in minority populations – Dr. Funmi Olopade

Supported early studies on genetic risk factors that contribute to the high incidence and mortality from breast cancer in young African American women.

BRCA2 mutation – Dr. David Goldgar and Dr. Susan Neuhausen

Funded the discovery of the founder BRCA2 617delT mutation in Ashkenazi Jews.



For more information, visit

<http://cdmrp.army.mil>

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